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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,420	01/26/2001	Sui Xiong Cai	1735.0440001/RWE/BEC	4240

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER

MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/769,420

Applicant(s)

CAI ET AL.

Examiner

Thomas McKenzie Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-43,46,47,51,52,58-61,71,76 and 79 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 79 is/are allowed.
- 6) ☒ Claim(s) 33-43,46,47,51,52,58,59,61,71 and 76 is/are rejected.
- 7) ☒ Claim(s) 60 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to an RCE filed on 5/19/03. There are twenty-two claims pending and twenty-two under consideration. Claims 58-61 and 79 are compound claims. Claim 71 is a composition claim. Claims 33-43, 46, 47, 51, 52, and 76 are use claims. This is the third action on the merits. The application concerns some nicotinamide compounds, compositions, and uses thereof.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/03 has been entered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The last compound listed in claim 59 has $R_6 =$

CF₃ and R₉ = hydrogen. There is no antecedent basis for this limitation in the parent claim 58, which does not allow for R₉ = hydrogen.

4. Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The last compound listed in claim 59 has R₆ = ClCH₂ and R₉ = hydrogen. There is no antecedent basis for this limitation neither in the either parent claim 60 nor in grandparent claim 58, which does not allow for R₉ = hydrogen.

5. Claims 33-43, 46, 47, 51, 52, and 76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast and cervical carcinomas, does not reasonably provide enablement for treating all other claimed cancers or inflammatory diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that

art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would treat any particular cancers or inflammatory disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different cancers or inflammatory diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating cancers or inflammatory diseases is found in the passage spanning line 10, page 23 to line 2, page 24, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 24, page 30 to line 31, page 32. There is no working example of any formulation, which would be required to practice Applicants invention. Doses required to practice their invention are described in lines 3-17, page 29. A 20,000-fold range of doses is recommended. Since no caspase activator has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is a *in vitro* assay described in the passage spanning line 11, page 55 to line 15, page 56 with data on thirty compounds. This assay

involved activation of enzymes in breast cancer cells but it is unclear if this assay is correlated to cancers generally. There are three additional *in vitro* assays in pages 58-61. These assays employ Jurkat, breast cancer, and HeLa cells respectively. There is data on two of the compounds described above. HeLa cells are described in Stedman's Medical Dictionary as a cervical carcinoma cell line.

c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in caspase related diseases is provided by Talanian (Ann. Reports. Med. Chem.). He states that in second complete paragraph page 278 and second paragraph page 279 caspase-1 (ICE) is a validated target and that inhibitors of this enzyme might be useful in treating the inflammatory disease sepsis. Applicants' compounds are activators, have the opposite effect of inhibitors, and may well make the inflammatory disease sepsis worse. Miller (Ann. Reports. Med. Chem.) states in the fourth paragraph, page 261 that it is unknown if blockage is therapeutically meaningful. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the millions of compounds of claim 33 as well as the dozens of listed diseases. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

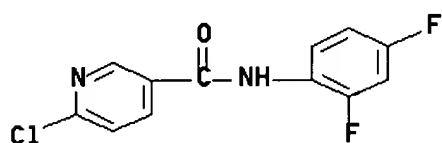
Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

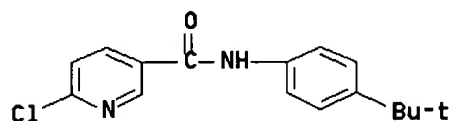
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mantlo ('884). There are still three compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_1 = R_3 =$ fluorine, $R_9 =$ chlorine, and $R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} =$ hydrogen. It has Registry Number 224817-04-3. Lines 32-34, column 84 of the reference states that 6-chloro-nicotinamides were used to prepare the compounds of Tables 8-11. The compound shown below therefore was used to make the entries of lines 28-45, column 86. The compound with $R_1 = R_3 =$ methoxyl was used form the entries spanning columns 86 and 87. The compound with $R_1 =$ hydrogen and $R_3 =$ fluorine was used to make the entries in lines 45-58, column 87. The compound with $R_{11} =$ methyl and $R_3 =$ chlorine was used to make the entries in lines 37-54, column 88.

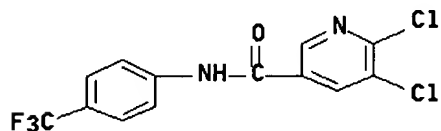


7. Claims 58 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Von der Saal (DE 3,804,346 A). The compound shown below fits formula (III) with $R_1 = R_3 =$ t-butyl, $R_9 =$ chlorine, and $R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} =$ hydrogen. It has Registry Number 125125-27-1 and is found in Example 35, lines

43-51, page 10 of the reference. Compositions are taught in claim 5 of the reference. Thus, claim 71 is anticipated.

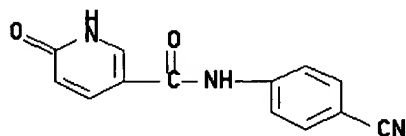


8. Claims 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Setliff (Proceedings of the Arkansas Academy of Science., 1995). There are two compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_3 = CF_3$, $R_9 = R_{10} = \text{chlorine}$, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 150115-54-1. The other compounds has $R_3 = \text{fluorine}$, $R_9 = R_{10} = \text{chlorine}$, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$ and has Registry Number 150115-51-8. The original reference has been ordered and the Chemical Abstracts printout is provided.

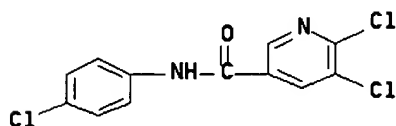


9. Claims 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Austel ('348). The compound shown below fits formula (III) with $R_3 = \text{cyano}$, $R_9 =$

hydroxyl, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 149354-21-2 and is found in lines 24-52, column 35 of the reference. Please note that the compound is drawn in its' tautomeric keto form.

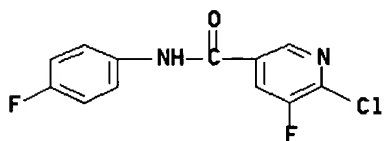


10. Claims 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Persons (Proceedings of the Arkansas Academy of Science.). There are three compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_3 = R_9 = R_{10} = \text{chlorine}$, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 165539-62-8. The other two compounds have Registry Numbers 150115-51-8 and 150115-54-1. They were discussed above. The original reference has been ordered and the Chemical Abstracts printout is provided.

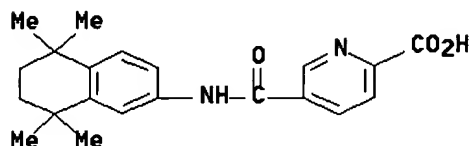


11. Claims 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Setliff (Proceedings of the Arkansas Academy of Science., 1995). There are two

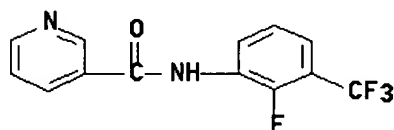
compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with R_3 = fluorine, R_9 = chlorine, R_{10} = fluorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{11}$ = hydrogen. It has Registry Number 179330-70-2. The other compound has $R_3 = CF_3$, R_9 = chlorine, R_{10} = fluorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11}$ = hydrogen and has Registry Number 179330-73-5. The original reference has been ordered and the Chemical Abstracts printout is provided.



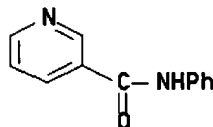
12. Claims 33-35, 42, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shudo (JP 06263702 A2). There are four compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_2 = R_3$ = fused carbocycle substituted by methyl, R_9 = carboxy, and $R_1 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11}$ = hydrogen. It has Registry Number 150115-54-1. Treatment of leukemia is taught in the abstract. A complete translation of the original reference has been ordered and the Chemical Abstracts printout is provided.



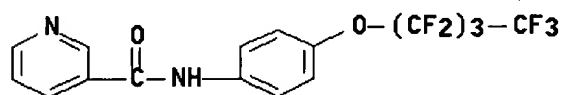
13. Claims 33, 36, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Klebanov (Fiziologicheski Aktivnye Veshchestv). There are eight compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_4 = CF_3$, $R_5 = \text{fluorine}$ and $R_1 = R_2 = R_3 = R_6 = R_7 = R_9 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 69135-93-9. Treatment of inflammation is taught in the abstract. A complete translation of the original reference has been ordered and the Chemical Abstracts printout is provided.



14. Claims 33, 36, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Bukhtiarova (Khimiko-Farmatsevticheskii Zhurnal). The compound shown below fits formula (III) with $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_9 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 69135-90-6. Treatment of inflammation is taught in the abstract. A complete translation of the original reference has been ordered and the Chemical Abstracts printout is provided.



15. Claims 33, 36, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Miryan (Khimiko-Farmatsevticheskii Zhurnal). The compound shown below fits formula (III) with R_3 = the haloalkoxy group pentafluoroethoxy and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_9 = R_{10} = R_{11}$ = hydrogen. It has Registry Number 69135-90-6. Treatment of edema and exudate is taught in the abstract. Both edema and exudate are a form of inflammation. A complete translation of the original reference has been ordered and the Chemical Abstracts printout is provided.

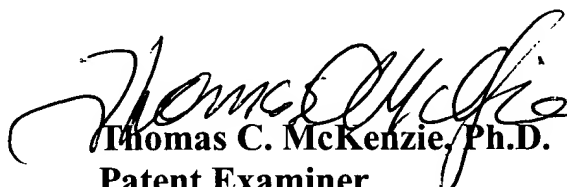


Allowable Subject Matter

16. Claim 79 is allowed. Claims 59 and 61 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK

